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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	//

DATE MAILED: 10/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/700,700	ALI ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *3 and 5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4, 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8, 9 .
4) ☒ Interview Summary (PTO-413) Paper No(s). 10 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's election with traverse of group I, claims 1-2, 4, 6, SEQ ID NO:1, species prostate cancer, in Paper No. 4 is acknowledged. The traversal is on the ground(s) that:

1) the Examiner suggestion that groups 1-14 lack the same or corresponding special technical feature under PCT rule 13.2 directly contracdicts both the Search report and the Written opinion issued by this same Examiner in the PCT application of which this case is the US national stage.

2) There is no burden for the Examiner to search because the full claim set was already searched and examined by the Examiner in the PCT application, and thus this restriction requirement does not meet the criteria set forth in MPEP 803, and

3) Concerning the species requirement, both prostate cancer and metastatic prostate cancer have already been searched by the same Examiner in the PCT application. Further, even if the search had not already been performed, inclusion of only two species in a generic claim can clearly not be considered to cause an unduly extensive or burdensome search.

This is not found persuasive because of the following reasons:

1) After review and reconsideration, this application clearly lacks unity, because groups 1-7 are drawn to methods using different prostate specific genes (PSG) of SEQ ID Nos:1-7, which do not share the same structure and function. Thus groups 1-7 are not linked by the same special technical feature. It is noted that a national stage application shall relate to one invention only or to a group of inventions so linked as to

form a single general inventive concept. Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features which define a contribution over the prior art. If there is no special technical feature, if multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(d).

2) Further, groups 8-14 are additional methods of use of SEQ ID Nos: 1-7. It is noted that if multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(d). Group I will be the main invention. After that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475(d).), and

3) Concerning species requirement of detecting prostate cancer and prostate metastasis, according to PCT Rule 13.2 and to the guidelines in Section (f)(i)(A) of Annex B of the PCT Administrative Instructions, all alternatives to a Markush group must have a common property or activity. Although the methods of groups 1-7 share a common feature of detecting prostate cancer cells, the species primary and metastatic prostate cancer are not regarded as being of similar nature because all the alternatives do not share common property or activity, i.e. primary and metastatic prostate cancers have different characteristics, and 4) Concerning the lack of burden for search, this is not a criteria for lack of unity requirement.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1-2, 4, 6, SEQ ID NO:1 and species primary prostate cancer and metastatic prostate cancer are examined in the instant application.

It is noted that the species metastatic prostate cancer has been rejoined with the species primary prostate cancer.

OBJECTION

1. Claims 1, 2, 4, 6 are objected to because part of claims 1, 2, 4, 6 are drawn to non-elected invention.

Claims 1, 2, 4, 6 are drawn to a method for diagnosing the presence of prostate cancer, or metastatic prostate cancer or the onset of metastatic prostate cancer in a patient comprising measuring levels of "PSG" in a sample of cells, tissue or bodily fluid obtained from the patient, and comparing the levels of "PSG" in a sample of cells, tissue or bodily fluid of the patient with the levels of "PSG" in a sample cells, tissue or bodily fluid of a control, wherein an increase in the levels of "PSG" in the patient versus the PSG level in the control is associated with the presence of prostate cancer, or metastatic prostate cancer or the onset of metastatic prostate cancer.

The specification discloses that "the levels of PSG" means levels of native mRNAs encoded by the gene comprising any of the polynucleotide sequences of SEQ ID NO:1-7, or levels of native proteins encoded thereby (p.5, lines 13-21).

Based on the disclosure of the specification, claims 1, 2, 4, 6 thus encompass a method for diagnosing the presence of prostate cancer or metastatic prostate cancer or

the onset of metastasis in a patient comprising measuring levels of mRNAs encoded by the gene comprising any of the polynucleotide sequences of SEQ ID NOs:1-7, or levels of native proteins encoded thereby.

Since Applicant elects SEQ ID NO:1 and since a method detecting the levels of each PSG constitutes a single invention, as stated in the restriction requirement of paper No:3, of 03/26/2002, claims 1, 2, 4, 6 encompass the non-elected methods of diagnosing the presence of prostate cancer or metastatic prostate cancer or the onset of metastasis in a patient comprising measuring levels of PSG comprising SEQ ID Nos: 2-6 or native proteins encoded thereby.

2. Claims 1, 2, 4 are objected to for the use of the language "associated". It is not clear how an increase in the measured levels of PSG is "associated" with the presence of prostate cancer. This objection could be obviated by amending the claim for example to replace "associated with" with "indicative of ".

3. Claim 6 is objected to because claim 6 is dependent on claims 3 and 5, which are drawn to non-elected inventions.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE OF ENABLEMENT

1. Claims 1-2, 4, 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for diagnosing the presence of prostate cancer, comprising measuring the levels of mRNAs of the polynucleotide of SEQ ID NO:1 in prostate cancer tissue, wherein an increase in the levels of said mRNA indicates the presence of prostate cancer, does not reasonably provide enablement for

a method for diagnosing prostate cancer, or metastatic prostate cancer or the onset of metastatic protate cancer, comprising measuring the "levels of PSG, which is the level of the PSG polypeptide encoded by the polynucleotide of SEQ ID NO:1", in "a sample of any cell, any tissue or any bodily fluid " obtained from a patient, wherein an increase in the levels of PSG is associated with the presence of prostate cancer or a cancer which has metastasized. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-2, 4, 6 are drawn to a method for diagnosing the presence of prostate cancer, or metastatic prostate cancer or the onset of metastasis of prostate cancer in a patient comprising measuring levels of PSG in a sample of cells, tissue or bodily fluid obtained from the patient, and comparing the levels of PSG in a sample of cells, tissue or bodily fluid of the patient with the levels of PSG in a sample cells, tissue or bodily fluid of a control, wherein an increase in the levels of PSG in the patient versus the PSG level in the control is associated with the presence of prostate cancer, or metastatic prostate cancer or prostate cancer which has metastasized.

A. Claims 1-2, 4, 6, as being drawn to a method for diagnosing the presence of prostate cancer, or metastatic prostate cancer or the onset of metastasis of prostate cancer in a patient comprising measuring "levels of PSG", are rejected under 35 USC 112, first paragraph.

The specification discloses that "the levels of PSG" means levels of native mRNAs encoded by the gene comprising any of the polynucleotide sequence of SEQ ID NO:1-7, or levels of native proteins encoded thereby (p.5, lines 13-21).

The specification discloses that the mRNA levels of PSG pro101 (SEQ ID NO:1) are highly specific for normal prostate tissues as compared to other normal tissues (p.14 and table 2 on page 14). The specification further discloses that mRNA levels of PSG pro101 (SEQ ID NO:1) are overexpressed in prostate cancer tissues as compared to matching normal adjacent tissue (p.15-17 and table 3 on pages 15-16).

There is no disclosure however of detecting the presence or overexpression of the polypeptide putatively encoded by the polynucleotide of SEQ ID NO:1 in prostate cancer or metastatic prostate cancer.

It is noted that in view of the definition of "levels of PSG" in the specification, the claims 1-2, 4, 6 encompass a method for diagnosing the presence of prostate cancer, or metastatic prostate cancer or the onset of metastasis of prostate cancer in a patient comprising measuring "levels of PSG", which is "the levels of the polypeptide encoded by SEQ ID NO:1" in a sample of cells, tissue or bodily fluid obtained from the patient, and comparing said levels of PSG, in a sample of cells, tissue or bodily fluid of the patient with the "levels of PSG", which is "the levels of the polypeptide encoded by SEQ ID NO:1", in a sample cells, tissue or bodily fluid of a control, wherein an increase in the levels of PSG in the patient versus the PSG levels in the control is associated with the presence of prostate cancer, or metastatic prostate cancer or prostate cancer which has metastasized.

One cannot extrapolate the teaching of the specification to the scope of the claims because there is no teaching of whether any protein product is actually produced, or even if translated, whether the overexpressed RNA leads to overexpressed protein. It is well known in the art that regulation of mRNA translation is one of the major regulatory steps in the control of gene expression (Jansen, M et al, 1995, Pediatric Res, 37 (6): 681-686). Further, those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said

patients being without mutations in the p53 gene. Yokota, J et al (Oncogene, 1988,Vol.3, pp. 471-475) teach that the retinoblasma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RB mRNA. Further, Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Hell et al (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Guo et al (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-ranslational level. Thus one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification.The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that PSG protein concentrations could be used in the claimed methods with a reasonable expectation of success.

Further, it is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of the overexpression in prostate cancer of the polypeptide encoded by the PSG polynucleotide of SEQ ID NO:1, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

B. Claims 1, 6, as being drawn to a method for diagnosing the presence of prostate cancer, comprising measuring levels of PSG in "a sample of cells, tissue or bodily fluid " obtained from a patient, are rejected under 35 USC 112, first paragraph.

The disclosure in the specification has been set forth above under section A.

i) Claims 1, 6 encompass a method for detecting primary or localized prostate cancer, comprising detecting overexpression of the mRNAs of the PSG of SEQ ID NO:1 in any tissue or any cell.

One cannot extrapolate the teaching of the specification to the scope of the claims. There is no correlation between overexpression of the mRNAs of the PSG of SEQ ID NO:1 in any tissue other than prostate tissue and overexpression of the mRNAs of the PSG of SEQ ID NO:1 in primary or localized prostate cancer tissues. It is well known in the art and as shown in the specification, expression of a gene in different tissues are independent of each other and/or is not necessarily at the same level in different tissue. For example, Willis RA, et al , 1998, teach that expression of the well known prostate specific antigen, PSA, is regulated in tissue-specific manner (Willis RA, et al, 1998, Intl J mol med (Greece), 1(2): 379-86). Lai, E et al, 1991, Trends in Biochem Sciences, 16 (11): 427-430, teach that the unique phenotype of each differentiated cell in an animal arises from selective expression of genes in a cell- or tissue-specific fashion, which is controlled primarily at the level of transcription. Similarly, the specification of the instant application discloses that the expression of the mRNAs of the PSG of SEQ ID NO:1 is highly prostate specific (p.14). Thus based on the teaching in the art and and in the specification, one would not expect that expression of the mRNAs of the PSG of SEQ ID NO:1 in any tissue other than prostate tissue is dependent on or related with overexpression of the mRNAs of the PSG of SEQ ID NO:1 in prostate cancer. In other words, overexpression of the polynucleotide of

SEQ ID NO:1 in prostate cancer tissue is not correlated with the expression of the polynucleotide of SEQ ID NO:1 in other tissues.

Further, overexpression of the mRNAs of the PSG of SEQ ID NO:1 in prostate cancer tissue as compared to normal prostate tissue appears to be specific to prostate, and thus it is cannot be predicted that the same phenomenon would also happen in other tissues in patients having primary or localized prostate cancer.

In addition, the specification lacks guidance on which tissue other than prostate cancer tissue in which overexpression of the mRNAs of the PSG of SEQ ID NO:1 is indicative of the presence of primary or localized prostate cancer. The specification lacks guidance on how to detect the presence of primary or localized prostate cancer based on overexpression of the mRNAs of the PSG of SEQ ID NO:1 in any tissue other than prostate cancer tissue.

Given the teaching of MPRP 2164.03 set forth above, and given the unpredictability of detection of the polynucleotide of SEQ ID NO:1 in any cell, or any tissue from patients with localized or primary prostate cancer, and the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and further in view that little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

ii) Further, claims 1, 6 also encompass a method for detecting primary prostate cancer, comprising detecting overexpression of the mRNAs of the PSG of SEQ ID NO:1 in any bodily fluid, such as bodily fluid from tracheobronchial tree, the gastrointestinal

tract, the bladder, cerebro-spinal fluid and the aqueous humor of the eye (Taber's cyclopedic medical dictionary, Clayton, T, ed. , 1989, Davis Co, Philadelphia, p. 231).

One cannot extrapolate the teaching of the specification to the scope of the claims. It is unpredictable that prostate cancer cells from localized prostate cancer, i.e. non-metastasizing prostate cancer could be detected in any bodily fluid, such as tracheobronchial tree, the gastrointesstinal tract, the bladder, cerebro-spinal fluid and the aqueous humor of the eye for the following reasons: One cannot predict that prostate cancer cells from localized prostate cancer, without having the properties necessary for metastasizing and colonizing, could reach and colonize these sites, in view of the fact that a large percentage of circulating prostate cancer cells, even having the metastasizing properties cannot survive in the environment outside of the prostate (US 5,674682,column 11, last paragraph).

Further, the specification does not disclose that prostate cancer cells from localized prostate cancer are found in any bodily fluid, such as tracheobronchial tree, the gastrointesstinal tract, the bladder, cerebro-spinal fluid and the aqueous humor of the eye. The specification does not disclose how to detect primary prostate cancer based on overexpression of the mRNAs of the PSG of SEQ ID NO:1 in any bodily fluid.

Given the teaching of MPRP 2164.03 set forth above, and given the unpredictability of detection of the polynucleotide of SEQ ID NO:1 in any bodily fluid from patients with localized or primary prostate cancer, and the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and further in view that little is known in the art about the claimed invention,

one of skill in the art would be forced into undue experimentation to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph rejection, claims 1, 2, 4, 6 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for diagnosing the presence of prostate cancer, comprising measuring the levels of mRNAs of the PSG of SEQ ID NO:1 in prostate cancer tissue, wherein an increase in the levels of said mRNA indicates the presence of prostate cancer, does not reasonably provide enablement for a method for diagnosing "metastatic prostate cancer or the onset of metastatic protate cancer", comprising measuring the levels of PSG in a sample of cells, tissue or bodily fluid obtained from a patient, wherein an increase in the levels of PSG is associated with the presence of prostate cancer or a cancer which has metastasized. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 6 are drawn to a method for diagnosing the presence of prostate cancer in a patient comprising measuring levels of PSG in a sample of cells, tissue or bodily fluid obtained from the patient, and comparing the levels of PSG in a sample of cells, tissue or bodily fluid of the patient with the levels of PSG in a sample cells, tissue or bodily fluid of a control, wherein an increase in the levels of PSG in the patient versus the PSG level in the control is associated with the presence of prostate cancer.

Claims 2, 4 are drawn to a method for diagnosing the presence of metastatic prostate cancer or the onset of metastasis of prostate cancer in a patient comprising

measuring levels of PSG in a sample of cells, tissue or bodily fluid obtained from the patient, and comparing the levels of PSG in a sample of cells, tissue or bodily fluid of the patient with the levels of PSG in a sample cells, tissue or bodily fluid of a control, wherein an increase in the levels of PSG in the patient versus the PSG level in the control is associated with the presence of metastatic prostate cancer or prostate cancer which has metastasized.

The specification discloses that the mRNA levels of PSG pro101 (SEQ ID NO:1) are highly specific for normal prostate tissues as compared to other normal tissues (p.14 and table 2 on page 14). The specification further discloses that mRNA levels of PSG pro101 (SEQ ID NO:1) are overexpressed in prostate cancer tissues as compared to matching normal adjacent tissue (p.15-17 and table 3 on pages 15-16).

It is noted that in table 3, the data presented do not differentiate between prostate cancer and metastatic prostate cancer, and therefore, it is reasonable to assume that the data presented in table 3 do not appear to be drawn to prostate cancer that is metastasized.

It is further noted that based on the disclosure in the specification that the mRNAs of the PSG of SEQ ID NO:1 is highly prostate specific (p.14), and in view that the language "prostate cancer" could be reasonably interpreted as either localized or metastatic prostate cancer, especially in view that the detecting in the claimed method in claims 1, 6 involves detecting the presence of the overexpression of SEQ ID NO:1 in any cell, tissue or any bodily fluid, the claims 1, 6 encompass a method for detecting metastatic prostate cancer by detecting overexpresssion of the mRNAs of the PSG

SEQ ID NO:1 in any cell from any tissue, or any tissue or bodily fluid, to which the prostate cancer cells have metastasized and colonized.

One cannot extrapolate the teaching of the specification to the scope of the claims, because it is unpredictable that SEQ ID NO:1 could be used for detecting metastasis or the onset of metastasis of prostate cancer. It is well known in the art that expression of a sequence could be lost or reduced during the progression toward metastasis, and thus it is unpredictable that metastasized prostate cells still express the claimed sequence of SEQ ID NO:1. For example, Kibel, AS et al, 2000, J urol, 164(1): 192-6 teach that gene expression in the chromosomal region 12p12-13 is different in primary and metastatic prostate cancer cells, and that inactivation in the chromosome region 12p12-13 occurs prior to metastasis of prostate cancer. Zhau, HE, 1994, J Cell Biochem, Suppl 19: 208-216, teach expression of various biomarkers associated with prostate cancer progression. Zhau et al further teach that in prostate cancer, subclones PC-3N35 cloned from primary and metastastatic sites (lymph node, kidney and bone), show difference in the levels of protein expression of various markers, such as c-erbB, vimentin, ICAM-1, cytokeratin, collagen IV between the parental PC-3N35 clone and its metastatic subclones (p.209 and table 1) and that the subline derived from the metastatic site lymph node has a 12p:17q translocation, whereas the bone-derived subline contains an isochromosome 7q (p.211, first column, first paragraph). Ren, C et al, 1998, Cancer Res, 58(6): 1285-90, teach a loss of expression of lysyl oxidase mRNA during progression to metastasis. Gingrich, JR et al, 1996, Cancer res, 56(18): 4096-4102 teach a loss of normal E-cadherin expression as primary tumors become less

differentiated and metastasize. Thus based on the teaching in the art, one cannot predict that metastasized prostate cells still express the claimed sequence of SEQ ID NO:1, and consequently one cannot predict that SEQ ID NO:1 could be used for detecting metastasis or the onset of metastasis of prostate cancer.

Further, the specification does not disclose how to make the invention, i.e. the specification does not disclose how to detect prostate metastatic cancer, or the onset of metastasis of prostate cancer, wherein the mRNAs of the PSG of SEQ ID NO:1 is detected and overexpressed in any type of cells or any tissue or bodily fluid.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of overexpression of SEQ ID NO:1 in prostate metastasis, and the use of SEQ ID NO:1 for detecting metastasis, or the onset of metastasis, the lack of adequate disclosure in the specification, and in view of the

complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

Patent Examiner

Augusts 28, 2003